REMARKS

This invention provides for, *inter alia,* a transdermal therapeutic system ("TTS") for delivery of active agents with moderate polarity comprising at least one polymer layer comprising microreservoirs wherein the polymer fraction in the polymer layer is at least 70% weight of polysiloxanes and the microreservoirs contain the active substance in dissolved form and the solvent comprises an ambiphilic solvent. Thus, the inventive TTS provides for an effective means for the transdermal delivery of active substance of moderate polarity.

Pursuant to 37 CFR 1.136(a) Applicants petition the Director to expand the time period to file a response by one (1) month, i.e., up to and including September 7, 2003. As this date is a Sunday, the extended due date is September 8, 2003. A check for $110.00 is enclosed. It is believed that no further fee is due. If, however, an additional fee is required, the Assistant Commissioner is authorized to charge such fee to Deposit Account 50-0320.

This Amendment cancels all the pending claims in favour of new claims 11 to 28. Claim 11 corresponds to former claim 1, claims 15, 16, 17, 18, 19 correspond to former claims 2, 3, 4, 5, 6, respectively. Claim 22 corresponds to former claim 7, claim 24 to former claim 8, claim 26 to former claim 9 and claim 27 to former claim 10. The remaining claims refer to the preferred embodiments of former claims 1, 6, 7 and 8. Thus, no new matter is added. As these changes are made for formal reasons and do not affect the scope of the originally claimed subject matter, the application of the doctrine of equivalents is not affected.

It is urged that the amendments to the claims overcome the rejection of claims 1 to 10 under 35 USC 112, second paragraph, moot and the withdrawal of the rejection is requested.

Claims 1, 3 to 10 stand rejected under 35 USC 103(a) for allegedly being unpatentable over WO 87/07138 ("World patent") in view of Oloff et al., US 5,071,657 ("Oloff") and claim 2

stands rejected under 35 USC 103(a) as being unpatentable over the World patent in view of Oloff as applied to claims 1, and 3 to 10 and further in view of Chien et al., US 5,145,682 ("Chien"). As these rejections rely on the same line of argument they will be discussed together.

Applicants respectfully urge that the rejection does not establish a *prima facie* case of obviousness since the World patent does not teach or suggest a TTS wherein the active substance is located in a microreservoir. Moreover, Oloff does not correct this deficiency since the prior publication discloses microdispersions wherein the gel comprises a silicone cross-linked elastomer, which is solid at room temperature, and is different from the polysiloxanes employed in the present invention, which are liquid. Hence, one would not arrive at the present invention by combining these prior publications as alleged in the rejection. Thus, reconsideration and withdrawal of these rejections are requested.

On pages 5 and 6 of the Office Action when describing the prior publication the rejection states that microdispersions "reads on microreservoirs." For the reasons that follow Applicants respectfully disagree.

The World patent describes on page 15, line 46 to page 16, line 20, how to prepare the pharmaceutical containing polymer mixtures. In that description, a polyol, such as polyethylene glycol, is used as a dispersing agent (p. 15, lines 55 – 56). A dispersing agent is not a dissolving agent. Further, on page 16, lines 16 to 21, the World patent indicates that the "amount of a dispersing agent can be varied from zero to about 50 percent." In the situation where the amount of the dispersion agent is 0% (cf. Ex. 1), the transdermal dosage unit according to World patent comprises a solid polymer matrix wherein the solid pharmaceutical agent (e.g. estradiol) is (micro) dispersed. In other words, the polymer matrix and the solid agent form a solid/ solid dispersion; i.e., other words, the active agent is essentially undissolved in the polymer. This

stands in contrast to the present invention wherein the active agent is dissolved in the solvent present in the microreservoir.

In the situation where the amount of dispersing agent is greater than zero, e.g. 10 to 50 percent polyol in an aqueous solution (page 16, lines 21 – 25), the polymer matrix that results is a fluid/ solid dispersion. Polyol itself and, particularly, a polyol-water mixture is a very poor solvent for lipophilic hormones, to which group sexual hormones, particularly estradiol and testosterone, belong. This position is directly supported in the disclosure on page 29 (Ex. 3, lines 5 – 24), where the mixture of the pharmaceutical agent and the aqueous solution is described as a paste (line 15). When the paste is mixed with a silicone elastomer a "homogeneous pharmaceutical/ polyethylene glycol/ polymer dispersion" is obtained (lines 21 – 23), in what appears to be a solid (pharmaceutical) /liquid (PEG-water)/solid (silicone elastomer) – dispersion. It is apparent from the discussion that only a small part of the steroidal pharmaceutical is dissolved in the aqueous polyethyleneglycol. The reason for this is due to the low solubility of steroids in aqueous solvents which results in the greater part of the steroids remaining solid and undissolved (cf. the disclosure on page 16, lines 53 – 57 "to dissolve and disperse the steroidal pharmaceutical in ... a selected aqueous solution of polyol").

In contrast thereto, the present invention provides for a TTS comprising at least one polymer layer containing microreservoirs (i.e. microholes), which are essentially free of water (cf. disclosure on page 5, line 20) and wherein an active substance of moderate polarity is dissolved in an ambiphilic, preferably dipolar organic solvent (cf. page 6, lines 1 – 2). The inventive system shows good active substance delivery during application on the skin because of high or constant thermodynamic activity (i.e. concentration) (cf. disclosure on page 9, lines 12 to 28). Hence, the Word patent does not suggest the present invention.

Further, it is respectfully urged that Oloff does not correct for this deficiency. Oloff provides for a TTS for the administration of active medicinal agents (e.g. steroid hormones), wherein the active agent is "dissolved to at least 50% in a nonflowable physiologically acceptable gel present in microdisperse distribution in a crosslinked silicone elastomer" (cf. col. 1, lines 36 – 41). While the solvents used for preparing the nonflowable gel (col. 2, lines 37 to 62) are similar in terms of their physical properties to the solvents as claimed in the present claims, the subject matter of the prior publication differs substantially from the present invention in that silicone elastomer (cf. the abstract), or more precisely, "a conventional, crosslinked silicone elastomer" (col. 3, lines 45 – 46) is used. Such silicones are preferably bi – component systems (col. 3, lines 50 – 52), wherein the components react after mixing and addition of a platinum catalyst to yield a three-dimensional crosslinked elastomer; this elastomer is not soluble in solvents. The resulting elastomer has very good cohesive properties and is nonflowable. Therefore, it is known as the ideal polymer for inclusion of fluids in the form of droplets as a separate phase.

In contrast thereto the present claims provide for a TTS, wherein the polymer layer consists to the extent of at least 70% (w/w) of a polysiloxane. The polysiloxane is solid at room temperature and is used in the preparation of the adhesive polymer layer according to the invention as a solution (cf. Examples 1 to 4). After removal of the solvent, these polymers behave like a very viscous fluid.

In view of these properties, it was surprising and could not be expected that the claimed (soluble) polymers contain, after mixing with a solution of a medicinal active substance in an ambiphilic solvent, the solution in the form of microreservoirs, without uniting the droplets to bigger drops, thereby decreasing the cohesive property of the polymers, and retention of the

microreservoir structure is even after removal of the solvent. As Chien does not correct for these deficiencies, it is urged that the rejection of claim 2 is also improper.

Thus, in view of the foregoing reconsideration of the rejection is requested.

Respectfully submitted,

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